Catheter Ablation of the Pulmonary Veins as Treatment for Atrial Fibrillation

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:
• Benefits are available in the member’s contract/certificate, and
• Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider the use of transcatheter radiofrequency ablation (RFA) of arrhythmogenic foci in the pulmonary veins as a treatment for atrial fibrillation for certain indications to be eligible for coverage.

Patient Selection Criteria
The use of transcatheter radiofrequency ablation (RFA) of arrhythmogenic foci in the pulmonary veins as a treatment for either of the following indications which have failed to respond to adequate trials of antiarrhythmic medications may be eligible for coverage in the following situations:
• Symptomatic paroxysmal or symptomatic persistent atrial fibrillation; or
• As an alternative to atrioventricular (AV) nodal ablation and pacemaker insertion in patients with class II or III congestive heart failure and symptomatic atrial fibrillation.

Based on review of available data, the Company may consider repeat radiofrequency ablations (RFAs) in patients with recurrence of atrial fibrillation and/or development of atrial flutter following the initial procedure may be considered eligible for coverage. (See Note)

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of transcatheter ablation of arrhythmogenic foci in the pulmonary veins as a treatment for atrial fibrillation for all other indications, except for specific cases of atrial fibrillation as noted above, to be investigational.*

Based on review of available data, the Company considers the use of transcatheter cryoablation of arrhythmogenic foci in the pulmonary veins as a treatment for atrial fibrillation to be investigational.*

Note:
Circumferential ablation of the pulmonary vein might be considered basically intra-arterial in location due to its close proximity to the pulmonary os and atria. Supraventricular tachycardias typically describe arrhythmias due to accessory pathways within the atria, such as Wolff-Parkinson-White syndrome or AV
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Nodal reentry arrhythmias. Although not consistently associated with tachycardia, strictly speaking, atrial fibrillation could be considered a type of supraventricular tachycardia.

As many as 30% of patients will require a follow-up (repeat) procedure due to recurrence of atrial fibrillation or to developing atrial flutter. In most of the published studies, success rates were based on having as many as three separate procedures, although these repeat procedures may be more limited than the initial procedure.

Background/Overview
Radiofrequency ablation using a percutaneous catheter-based approach is widely used to treat supraventricular arrhythmias. Atrial fibrillation frequently arises from an abnormal focus at or near the junction of the pulmonary veins and the left atrium, thus leading to the feasibility of more focused ablation techniques directed at these structures. Catheter-based ablation, using both RFA and cryoablation, is being studied in the treatment of various types of atrial fibrillation.

Atrial fibrillation is the most common cardiac arrhythmia, with a prevalence estimated at 0.4% of the population, increasing with age. The underlying mechanism of atrial fibrillation involves an interplay between electrical triggering events and the myocardial substrate that permits propagation and maintenance of the aberrant electrical circuit. The most common focal trigger of atrial fibrillation appears to be located within the cardiac muscle that extends into the pulmonary veins.

Atrial fibrillation accounts for approximately one-third of hospitalizations for cardiac rhythm disturbances. Symptoms of atrial fibrillation, i.e., palpitations, decreased exercise tolerance, and dyspnea, are primarily related to poorly controlled or irregular heart rate. The loss of AV synchrony results in a decreased cardiac output, which can be significant in patients with compromised cardiac function. In addition, patients with atrial fibrillation are at higher risk for stroke, and anticoagulation is typically recommended. Atrial fibrillation is also associated with other cardiac conditions, such as valvular heart disease, heart failure, hypertension, and diabetes. Although episodes of atrial fibrillation can be converted to normal sinus rhythm using either pharmacologic or electroshock conversion, the natural history of atrial fibrillation is one of recurrence, thought to be related to fibrillation-induced anatomic and electrical remodeling of the atria.

Atrial fibrillation can be subdivided into three types:

- Paroxysmal (episodes that last fewer than seven days and are self-terminating),
- Persistent (episodes that last for more than seven days and can be terminated pharmacologically or by electrical cardioversion), or
- Permanent.

Treatment strategies can be broadly subdivided into rate control, in which only the ventricular rate is controlled and the atria are allowed to fibrillate, or rhythm control, in which there is an attempt to re-establish and maintain normal sinus rhythm. Rhythm control has long been considered an important treatment goal for management of atrial fibrillation, although its primacy has recently been challenged by the results of several randomized trials that reported that pharmacologically maintained rhythm control offered no improvement in mortality or cardiovascular morbidity compared to rate control.
Currently, the main indications for a rhythm control are for patients with paroxysmal or persistent atrial fibrillation who have hemodynamic compromise associated with episodes of atrial fibrillation or who have bothersome symptoms despite adequate rate control. A rhythm-control strategy involves initial pharmacologic or electronic cardioversion, followed by pharmacologic treatment to maintain normal sinus rhythm. However, antiarrhythmic medications are often not effective in maintaining sinus rhythm. As a result, episodes of recurrent atrial fibrillation are typical, and patients with persistent atrial fibrillation may require multiple episodes of cardioversion. Implantable atrial defibrillators, which are designed to detect and terminate an episode of atrial fibrillation, are an alternative in patients otherwise requiring serial cardioversions, but these have not yet achieved widespread use. Patients with paroxysmal atrial fibrillation, by definition, do not require cardioversion but may be treated pharmacologically to prevent further arrhythmic episodes.

Treatment of permanent atrial fibrillation focuses on rate control, using either pharmacologic therapy or ablation of the AV node, followed by ventricular pacing. Although AV nodal ablation produces symptomatic improvement, it does entail lifelong anticoagulation (due to the ongoing fibrillation of the atria), loss of AV synchrony, and lifelong pacemaker dependency. Implantable defibrillators are contraindicated in patients with permanent atrial fibrillation.

The cited treatment options are not considered curative. A variety of ablative procedures have been investigated as potentially curative approaches, or perhaps modifying the arrhythmia such that drug therapy becomes more effective. Ablative approaches focus on interruption of the electrical pathways that contribute to atrial fibrillation through modifying the arrhythmia triggers and/or the myocardial substrate that maintains the aberrant rhythm. The Maze procedure, an open surgical procedure often combined with other cardiac surgeries (i.e., valve repair), is an ablative procedure that involves sequential atriotomy incisions designed to create electrical barriers that prevent the maintenance of atrial fibrillation. Because of the highly invasive nature of this procedure, it is currently mainly reserved for patients who are undergoing open heart surgery for other reasons, such as valve repair or coronary artery bypass grafting.

Radiofrequency ablation using a percutaneous catheter-based approach is a widely used technique for a variety of supraventricular arrhythmias, in which intracardiac mapping identifies a discrete arrhythmogenic focus that is the target of ablation. The situation is more complex for atrial fibrillation, since there is not a single arrhythmogenic focus. Since the inception of ablation techniques in the early 1990s, there has been a progressive understanding of the underlying electrical pathways in the heart that are associated with atrial fibrillation. In the late 1990s, it was recognized that atrial fibrillation most frequently arose from an abnormal focus at or near the junction of the pulmonary veins and the left atrium, thus leading to the feasibility of more focused, percutaneous ablation techniques. The basic strategies that have emerged for focal ablation within the pulmonary veins, as identified by electrophysiologic mapping, are segmental ostial ablation guided by pulmonary vein potential (electrical approach), or circumferential pulmonary vein ablation (anatomic approach). Circumferential pulmonary vein ablation is the most commonly used approach at the present time. The procedure also can be done using cryoablation technology.

Repeat procedures following an initial RFA are commonly performed if atrial fibrillation recurs or if atrial flutter develops post-procedure. The need for repeat procedures may, in part, depend on clinical
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characteristics of the patient (age, persistent vs. paroxysmal atrial fibrillation, atrial dilatation, etc.) and the type of initial ablation performed. Repeat procedures are generally more limited than the initial procedure. For example, in cases where electrical reconnections occur as a result of incomplete ablation lines, a “touch up” procedure is done to correct gaps in the original ablation. In other cases where atrial flutter develops following ablation, a “flutter ablation” is performed, which is more limited than the original atrial fibrillation ablation procedure. A number of clinical and demographic factors have been associated with the need for a second procedure, including age, length of atrial fibrillation, permanent atrial fibrillation, left atrial size, and left-ventricular ejection fraction.

FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration (FDA)
In February 2009, the NAVISTAR™ THERMOCOOL™ Irrigated Deflectable Diagnostic/Ablation Catheter and EZ Steer ThermoCool NAV Catheter (Biosense Webster Inc.) were approved by the FDA through the pre-market approval (PMA) process for “catheter-based cardiac electrophysiological mapping (stimulating and recording), and when used with the Stockert 70 generator, for the treatment of a) Type I atrial flutter in patients age 18 or older; b) recurrent drug/device refractory sustained monomorphic ventricular tachycardia (VT) due to prior myocardial infarction (MI) in adults; c) drug refractory recurrent symptomatic paroxysmal atrial fibrillation, when used with compatible 3-dimensional electroanatomic mapping systems.” (For RFA.)

In December 2010, Medtronic’s Arctic Front™ Cardiac CryoAblation Catheter and CryoConsole were approved by the FDA for the “treatment of drug refractory recurrent symptomatic paroxysmal atrial fibrillation.” In addition, Medtronic’s Freezor™ MAX Cardiac CryoAblation Catheter was approved as an adjunctive device to be used in conjunction with the Arctic Front system for “gap cryoablation to complete electrical isolation of the pulmonary veins, cryoablation of focal trigger sites, and creation of ablation line between the inferior vena cava and the tricuspid valve.” (For cryoablation.)

In addition, the FDA has also granted PMA approval to numerous catheter ablation systems for other ablation therapy for arrhythmias such as supraventricular tachycardia, atrial flutter, and VT.

Rationale/Source
In patients with paroxysmal or persistent atrial fibrillation, pulmonary vein ablation may be considered an alternative to drug therapy. In patients with permanent atrial fibrillation, pulmonary vein ablation may be considered an alternative to drug therapy or to AV nodal ablation and pacing. For all types of atrial fibrillation, it is possible that pulmonary vein ablation may not be curative as a sole treatment but might alter the underlying myocardial triggers or substrate in such a way that subsequent pharmacologic therapy may become more effective.

There is ongoing controversy regarding the relative benefits of rhythm versus rate control in atrial fibrillation, which underlies the evaluation of evidence on catheter ablation. Randomized trials of pharmacologic therapies have not demonstrated the superiority of rhythm versus rate control. However, the apparent equivalency of these two strategies with pharmacologic therapy cannot be extrapolated to the rhythm control achieved with ablation. Antiarrhythmic medications used for rhythm control are only partially effective and have serious complications, including proarrhythmic properties that can be lethal. Therefore,
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Nonpharmacologic strategies for rhythm control have the potential to achieve superior outcomes than have been seen with pharmacologic strategies.

**Outcome Assessment in Atrial Fibrillation**

A variety of outcomes for treatment of atrial fibrillation may be considered. The mortality and morbidity related to atrial fibrillation, such as cardiovascular mortality, stroke, and heart failure, are the most important clinical outcomes. However, these are uncommon events, and currently available trials are not powered to detect differences in these outcomes. Quality of life (QOL) is also an important outcome, as these measures reflect important manifestations of atrial fibrillation, such as symptoms and reduced exercise tolerance. Atrial fibrillation has been shown to be associated with lower QOL scores, and maintenance of sinus rhythm has been associated with higher QOL scores for patients with paroxysmal atrial fibrillation.

Recurrence of atrial fibrillation is a more problematic outcome measure, since the intermittent and often transient nature of recurrences makes accurate measurement difficult. This outcome measure has been reported in different ways. For example, the proportion of patients in sinus rhythm at the end of the study, the time to first recurrence, and the number of recurrences within a time period have been reported. A recent publication highlights the difficulties in measuring atrial fibrillation recurrence and recommends a measure of atrial fibrillation “burden,” defined as the percentage of time an individual is in atrial fibrillation, as the optimal measure of treatment efficacy. However, this parameter requires continuous monitoring over a relatively long period of time, which is inconvenient for patients, resource intensive, and usually not pragmatic in patients who do not already have an implanted pacemaker.

Recommendations for outcome assessment in trials of atrial fibrillation treatment were included in the 2006 American College of Cardiology/American Heart Association practice guidelines for the treatment of atrial fibrillation. These guidelines pointed out that the appropriate endpoints for evaluation of treatment efficacy in patients with paroxysmal or persistent atrial fibrillation have little in common. For example, in studies of persistent atrial fibrillation, the proportion of patients in sinus rhythm at the end of follow-up is a useful endpoint, but this is a less useful measure in studies of paroxysmal atrial fibrillation. Given all these variables, ideally, controlled clinical trials would report a range of outcomes (including QOL) and complications in homogeneous patient groups and compare to the most relevant treatment alternatives, such as pharmacologic therapy; defibrillator therapy; and AV nodal ablation, depending on the classification of atrial fibrillation (paroxysmal, persistent, or permanent).

**Radiofrequency Ablation of the Pulmonary Veins**

**Systematic Reviews**

The literature review for this policy was originally based on a 2008 TEC Assessment. Six randomized, controlled trials (RCTs) met the inclusion criteria for this TEC Assessment. The trials differed in their patient populations, the specific catheter ablation techniques used, and the comparisons made. The trials addressed 3 distinct indications for catheter ablation: 1) patients with paroxysmal atrial fibrillation, as a first-line treatment option (n = 1 trial); 2) patients with symptomatic paroxysmal or persistent atrial fibrillation who have failed treatment with antiarrhythmic drugs (n = 4 trials); and 3) patients with symptomatic atrial fibrillation and heart failure who have failed treatment with standard medications for rate control and who would otherwise be considered for AV nodal ablation and pacemaker insertion (n = 1 trial).
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All six trials reported that maintenance of sinus rhythm was improved for the catheter ablation group. Recurrence rates of atrial fibrillation at one year ranged from 11–44% for the catheter ablation groups in these trials, compared with 63–96% for the medication groups. Four of the 6 trials reported QOL outcomes. One of these only reported within-group comparisons, as opposed to between-group comparisons. The other three trials reported improvements in QOL associated with catheter ablation. These QOL measures were self-reported, and since both trials were unblinded, there is the possibility of reporting bias due to placebo effect.

None of the available trials reported meaningful data on cardiovascular morbidity and mortality associated with atrial fibrillation. The Assessment concluded that radiofrequency catheter ablation is more effective than medications in maintaining sinus rhythm across a wide spectrum of patients with atrial fibrillation and across different variations of catheter ablation. The evidence on QOL is suggestive, but not definitive, of a benefit for patients undergoing catheter ablation. For other outcomes, the evidence did not permit conclusions. It was not possible to estimate the rate of serious complications, such as pulmonary vein stenosis, cardiac tamponade, or atrio-esophageal fistula with precision given the limited number of patients in the trials and the continued evolution of the technique. However, the rate of serious complications is expected to be low, likely in the 1–5% range.

Based on these findings, TEC criteria were met for 2 indications: patients with symptomatic paroxysmal or persistent atrial fibrillation who have failed treatment with antiarrhythmic drugs and patients with symptomatic atrial fibrillation and heart failure who have failed treatment with standard medications for rate control and who would otherwise be considered for AV nodal ablation and pacemaker insertion. For the first indication, the conclusion followed from the premise that reducing episodes of recurrent atrial fibrillation for this population will reduce or eliminate the symptoms associated with episodes of atrial fibrillation. For the other indication, the single multicenter RCT available was judged sufficient to conclude that catheter ablation improved outcomes compared to the alternative, AV nodal ablation and pacemaker insertion. While this trial was relatively small, it was judged to be otherwise of high quality and reported improvements of a relatively large magnitude across a range of clinically important outcome measures, including QOL, exercise tolerance, left-ventricular ejection fraction, and maintenance of sinus rhythm.

A Cochrane Review on catheter ablation for paroxysmal and persistent atrial fibrillation was published in 2012. This review included 7 RCTs of catheter ablation versus medical therapy. Main conclusions were that catheter ablation was superior at reducing the recurrence of atrial fibrillation (risk ratio [RR]: 0.27, 95% confidence interval [CI]: 0.18-0.41) but that there were no differences in mortality (RR: 0.50, 95% CI: 0.04-5.65), embolic complications (RR: 1.01, 95% CI: 0.18-5.68), or death from thromboembolism (RR: 3.04, 95% CI: 0.13-73.4).

Two systematic reviews published in 2008 summarized and synthesized the RCT evidence on catheter ablation versus alternate therapy. These reviews included 4 of the 6 trials reviewed for the TEC Assessment. Noheria et al. included 3 of these 4 RCTs, as well as an additional small RCT of 30 patients not included in the TEC Assessment. Gjesdal et al. included 5 RCTs in their analysis, including the 4 trials in the Noheria et al. systematic review, and 1 additional trial (included in the TEC Assessment) that compared catheter ablation plus antiarrhythmic drugs with antiarrhythmic drugs alone.
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Both of these systematic reviews concluded that catheter ablation was more effective than pharmacologic treatment in maintaining normal sinus rhythm. In combined analysis, Noheria et al. reported atrial-fibrillation-free survival at 1 year to be 75.7% in the catheter ablation group compared to 18.8% in the comparison group. The relative risk for maintaining sinus rhythm was 3.73 (95% CI: 2.47–5.63) for the catheter-ablation group compared to alternative treatment. Gjesdal et al. concluded that the available evidence was of moderate quality and consistent in reporting that atrial-fibrillation-free survival was superior for the catheter ablation group. However, due to unexplained heterogeneity, these authors did not perform a combined analysis.

Additional Randomized Controlled Trials
Since the TEC Assessment, three additional RCTs comparing RFA versus pharmacologic treatment have been identified. Wilber et al. enrolled 167 patients who had failed at least one antiarrhythmic medication and had at least 3 atrial fibrillation episodes in the prior 6 months. Patients were randomly assigned to either catheter ablation or continued drug therapy and followed for 9 months. At the end of follow-up, 66% of patients in the ablation group were free of recurrent atrial fibrillation compared to 16% of patients in the medication group. Adverse events related to treatment occurred in 4.9% (5/103) of patients treated with ablation and in 8.8% (5/57) of patients treated with medications.

Forleo et al. randomly assigned 70 patients with type 2 diabetes and atrial fibrillation to either RFA or an antiarrhythmic medication. Follow-up was for 1 year, with the primary outcome being recurrence of atrial fibrillation. At the end of the trial, 42.9% of patients in the medication group were free of atrial fibrillation compared to 80% of patients in the ablation group. There was also a significant improvement in QOL for patients in the ablation group. Adverse events from medications occurred in 17.2% (6/35) patients, whereas complications from ablation occurred in 2.9% (1/35).

An RCT of RFA ablation as the initial therapy for paroxysmal atrial fibrillation was published in 2012. A total of 294 patients were randomized to initial treatment with catheter ablation or pharmacologic therapy. Patients were followed for up to 24 months for the primary outcomes of burden of atrial fibrillation (percent of time in atrial fibrillation on Holter monitor) at each time point and cumulative burden of atrial fibrillation over all time points. For the individual time points, the burden of atrial fibrillation was lower in the catheter ablation group at 24 months (9% versus 18%, p = 0.007), but not at other time points. The cumulative burden did not differ significantly for the catheter ablation group compared to pharmacologic therapy (90th percentile of cumulative burden, 13% versus 19%, p = 0.10). The secondary outcome of percent of patients free from atrial fibrillation at 24 months was greater for the catheter ablation group (85% vs. 71%, p = 0.004), as was the secondary outcome of freedom from symptomatic atrial fibrillation (93% vs. 84%, p = 0.01). There was one death in the ablation group due to a procedural-related stroke, and there were 3 patients in the ablation group who developed cardiac tamponade following the procedure.

Longer-term Outcomes.
The available RCTs mainly report on short-term outcomes up to 1 year and, therefore, do not evaluate the rate of late recurrences after 1 year. Longer-term outcomes have been reported by several authors. These studies generally report rates of early recurrence in the range of 20-30%, requiring repeat ablations. Rates of longer-term recurrence are lower if early recurrence does not occur, in the range of 1-2% per year.
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Hussein et al. reported on 831 patients who were treated in 2005, with a median follow-up of 55 months. During the first year following ablation, 23.8% had a recurrence of atrial fibrillation. During the remaining follow-up, recurrences occurred in 8.9% additional patients. The overall rate of arrhythmia-free and off drugs was 79.4% at 55 months. An additional 10.5% of patients were arrhythmia-free on drugs, for a total rate of 89.9% clinical improvement.

Several smaller studies have also reported longer-term follow-up. Weerasooriya et al. reported 5-year follow-up in 100 patients treated with catheter ablation. Recurrences were most common within the first 6 months, with repeat procedures being common during that period. At 1, 2, and 5 years post-ablation, arrhythmia-free survival was 87%, 81%, and 63%, respectively. Tzou et al. reported long-term follow-up for 123 patients who had a previous successful ablation, defined as free of atrial fibrillation at 1 year. At 3 years of follow-up, 85% of patients were still free of atrial fibrillation and off of all medications, and at 5 years, 71% remained free of atrial fibrillation. The authors estimated a late recurrence rate of approximately 7% per year for patients with an initial successful procedure. In a similar study, Bertaglia et al. reported outcomes after 6 years of follow-up for 229 patients who had a single, successful ablation. At 1-year follow-up, 77% of patients (177/229) were free of atrial fibrillation and off of all medications. After a mean additional follow-up of 49.7 +/- 13.3 months for these 177 patients, 58% remained free of atrial fibrillation. Sawhney et al. reported 5-year success rates in 71 patients who underwent ablation in 2002 or 2003. Freedom from symptomatic atrial fibrillation off medications was achieved in 86% of patients at 1 year, 79% at 2 years, and 56% at 5 years. A substantial minority of patients (22.5%) had recurrence at times greater than 2 years post-ablation.

Conclusions
Numerous RCTs of RFA of the pulmonary veins versus medical management report that freedom from atrial fibrillation at 1 year is higher with RFA compared to medical management. The trials mainly include patients who have failed anti-arrhythmic medications, although 2 trials treat patients with paroxysmal atrial fibrillation as initial treatment. These studies report that a majority of patients undergoing RFA are free of atrial fibrillation at 1 year. Quality of life is also improved in these trials for patients undergoing catheter ablation. A smaller number of studies evaluate outcomes longer than 1 year and report that late recurrences occur up to 5 years but are uncommon after the first year. Complications from RFA are reported at low rates in the RCTs, but the numbers of patients in these trials are too low to accurately estimate rates of uncommon events. There is a lack of data on clinical outcomes other than freedom from atrial fibrillation. Larger RCTs are underway to evaluate long-term clinical outcomes such as stroke and mortality.

Cryoablation of the Pulmonary Veins
A number of studies reported outcomes of ablation using cryoablation. These were mainly case series reporting success rates in the range of that reported for RFA. One small matched analysis compared 20 patients undergoing cryoablation with 20 patients undergoing RFA, matched for age, gender, left ventricular ejection fraction, and atrial fibrillation history. Freedom from atrial fibrillation at 6 months was 55% for the cryoablation group, compared to 45% for the RFA group, a difference that was not significantly different.

Results of the STOP-AF trial, an RCT of cryoablation versus antiarrhythmic medications, were presented at the March 2010 American College of Cardiology meeting, but as of February 2012, results have not yet

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been published in the peer-reviewed literature. This study enrolled 245 patients with paroxysmal atrial fibrillation who had failed a median of 1.2 medications. At 1-year follow-up, 69.9% of patients in the ablation group were free of atrial fibrillation versus 7.3% in the medication group. There was also a significantly greater reduction in symptoms for the ablation group. Serious adverse events were reported in 3.1% of ablation patients. Phrenic nerve injury occurred at a rate of 13.5%, with 86% resolved at 12 months.

A meta-analysis of studies of cryoablation was published in 2011. This analysis included the STOP-AF results in abstract form and a total of 22 other non-randomized studies, primarily case series. Procedural success was reported in over 98% of cases. At 1 year, the rates of success, as defined by no recurrent atrial fibrillation, were 73% (95% CI: 69-77%) for paroxysmal atrial fibrillation and 60% (95% CI: 54-66%) for persistent atrial fibrillation. Complications were inconsistently reported among the available studies. The most common complication reported was phrenic nerve palsy, which occurred in 6.4% of patients. Other rates of reported complications were pericardial effusion or tamponade (1.5%), groin complications at insertion site (1.8%), stroke (0.3%), and pulmonic stenosis (0.9%).

There are ongoing trials of cryoablation versus RFA for atrial fibrillation. The FreezeAF trial is a randomized controlled noninferiority trial comparing cryoablation to RFA for patients with paroxysmal atrial fibrillation. Enrollment of 244 patients is planned, and patients will be followed for at least 1 year. The primary outcome is freedom from atrial fibrillation off all drugs. Secondary outcomes include longer-term success rates, procedural data, and cost-effectiveness. The MACPAF trial will compare outcomes of RFA and cryoablation in 108 patients with paroxysmal atrial fibrillation, with a focus on adverse events including cerebral thromboembolism through the use of serial magnetic resonance imaging (MRIs) and neuro-psychological testing.

Conclusions
Numerous case series of cryoablation report uncontrolled outcomes of this technique. One RCT of cryoablation versus medical management has been completed and is available in abstract form; this trial reports freedom from atrial fibrillation that is in the range of results reported for RFA, but on the low side. Similar types of complications are reported following cryoablation as compared to RFA, but the available evidence is not sufficient to conclude whether rates of adverse events are reduced with cryoablation. Therefore, the evidence is not sufficient to determine the comparative efficacy of cryoablation compared to RFA. Ongoing RCTs are currently addressing this question.

Repeat Procedures
Repeated procedures for recurrent atrial fibrillation or atrial flutter were commonly performed in most of the clinical trials included in this policy statement. Of the 7 RCTs reviewed, only 2 did not include repeated procedures. In the other 5 studies, one or more repeated procedures were allowed, and success rates reported generally incorporated the results of up to 3 procedures. In 3 studies that reported these data, repeated procedures were performed in 9%, 20%, and 32% of patients randomized to ablation. Stabile et al. did not report specifics on how many patients actually underwent repeated procedures, but limited data in the publication indicated that up to 30% of treated patients were eligible for repeated procedures. In the Jais et al. study, patients underwent a mean of 1.8 procedures per patient and a median of 2 procedures per
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patient, indicating that approximately 50% of patients in the ablation group underwent at least one repeated procedure.

Because of this high rate of repeated procedures, the results reported in these studies do not reflect the success of a single procedure. Rather, they more accurately estimate the success of an ablation strategy that includes repeated procedures for recurrences that occur within the first year of treatment. Nonrandomized evidence suggests that early reablation increases the success of the procedure, when defined as maintenance of sinus rhythm at 1 year. There is variability in the protocol for when repeated procedures should be performed. There is also uncertainty concerning other details on repeated procedures, such as how soon after the initial procedure it should be done, the threshold of atrial fibrillation recurrence that should prompt a repeat, and whether medications should be tried prior to a repeated procedure.

Complications
In addition to the complication rates reported in available clinical trials and case series, there have been a number of database studies and post-marketing surveillance that report complications in larger numbers of patients than are in the clinical trials. A representative sample of these studies is discussed below.

Waldo et al. reported the results of an FDA-directed post-marketing safety study involving 1,275 patients from 6 prospective, multicenter studies of RFA ablation using an open-irrigated catheter. A total of 4.9% (63/1,275) of patients experienced any acute serious complication within 7 days of the procedure. Vascular access complications were most common, ranging from 0.5% to 4.7% across the 6 studies. Exacerbations of heart failure occurred in 1.5% of patients, and 2 patients experienced cardiac tamponade. There were no strokes or transient ischemic attacks (TIAs) reported post-procedure.

Shah et al. used data from a California hospital database to evaluate complications in 4,156 patients who underwent catheter ablation for atrial fibrillation. Major complications occurred in 5.1% (211/4,156) of patients, with approximately half of these (2.6%, 110/4,156) consisting of hemorrhage or hematoma at the vascular entry site. The most common cardiac complication was cardiac perforation and/or tamponade, which occurred in 2.5% (104/4,156) of patients. Less common rates of serious adverse events included death (0.02%), stroke/TIA (0.31%), and pneumothorax/hemothorax (0.1%). Factors that were predictive of complications were female gender, older age, prior hospitalizations for atrial fibrillation, and less hospital experience with ablation.

In a study of Medicare beneficiaries, Ellis et al. identified 6,065 admissions from 168 hospitals in which RFA for atrial fibrillation was performed. The total rate of in-hospital complications was 9.1%, with vascular complications accounting for over half of the total complications at a rate of 5.7%. The mortality rate was 0.4%, and 0.6% of patients suffered a stroke or TIA. Perforation or tamponade occurred in 3.1% of patients and pneumothorax occurred in 0.4% of patients. The presence of chronic obstructive pulmonary disease (COPD) or unstable angina was associated with a higher risk of complications, while obesity and hyperlipidemia were associated with a lower risk. Age and hospital volume were not significant predictors of risk, but low hospital volume was a significant predictor of in-hospital death.
Complications of catheter ablation were reported in a large cohort of 1,000 patients undergoing ablation at a high-volume center in Europe. There were no deaths definitely attributable to the procedure, but there were 2 deaths of uncertain cause within the first 30 days following ablation. Overall, 3.9% of patients had a major complication resulting from the procedure. Tamponade was the most serious life-threatening complication, occurring in 1.3% of patients. Major vascular complications occurred in 1.1%. Thromboembolism, cerebrovascular accident/TIA, atrio-esophageal fistula, and endocarditis were all reported complications that occurred at a rate of less than 1%.

Cappato et al. performed a multicenter, retrospective case series to estimate the overall mortality rate following ablation. Data were collected on 32,569 patients from 162 clinical centers worldwide. There were 32 deaths reported, for a mortality rate of 0.98 per 1,000 patients. The most common causes of death were tamponade (n = 8), stroke (n = 5), atrio-esophageal fistula (n = 5), and pneumonia (n = 2).

Conclusions
Several large, database studies estimate the rate of adverse events from catheter ablation in the clinical care setting. The range of major adverse events in these studies is from 4-9%. Deaths have been reported and occur at rates less than 1%. Vascular complications at the groin site are the most common adverse events, occurring at rates of up to 5%. Serious cardiovascular adverse events such as tamponade and stroke occur uncommonly, at rates of approximately 1% or lower.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers
In response to requests, input was received from 2 physician specialty societies (3 reviewers) and 2 academic medical centers. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. While the input was mixed, there was general agreement with the policy statements. One reviewer commented that use of cryoablation may have a specific role when ablation targets are close to the AV node.

Summary
Results of randomized, controlled trials that compare RFA with antiarrhythmic medications report that freedom from atrial fibrillation is more likely following ablation compared with medications. Results of long-term follow-up of 5 to 6 years following ablation demonstrate that late recurrences continue to occur in patients who are free of atrial fibrillation at 1 year. However, the majority of patients who are atrial-fibrillation-free at 1 year remain atrial-fibrillation-free at 5 to 6 years. Rates of complications following ablation remain uncertain; evidence for this update supports a serious complication rate in the range of 4-9% and a mortality rate of less than 1%. As a result, RFA of the pulmonary veins is considered eligible for coverage for symptomatic paroxysmal or persistent atrial fibrillation, when antiarrhythmic medications have failed to adequately control symptoms.

Case series of cryoablation report success rates in the range seen for RFA, and the preliminary results of one randomized, controlled trial report that cryoablation is more effective than medications. However, rates of success with cryoablation are on the lower end of results seen when using radiofrequency. It is not yet
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possible to determine whether outcomes of cryoablation are similar to that for RFA. Randomized, controlled trials comparing the two techniques are currently underway. Thus, cryoablation of the pulmonary veins is considered investigational.

Repeat procedures are commonly within the first year after initial ablation and are associated with an incremental improvement in maintenance of sinus rhythm. These repeat procedures are of a more limited nature compared to the initial ablation, targeting specific areas where ablation may not be complete, and/or a focused ablation for treatment of post-ablation atrial flutter. These repeat procedures, generally up to 2 repeat ablations, may therefore be considered eligible for coverage.

References
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Policy History
Original Effective Date: 09/15/2010
Current Effective Date: 10/16/2013
09/09/2010 Medical Policy Committee review
09/01/2011 Medical Policy Committee review
09/14/2011 Medical Policy Implementation Committee approval. Coverage statements edited for clarity, but no change in intent of coverage statements. Note added at the end of coverage section.
10/11/2012 Medical Policy Committee review
01/23/2013 Coding updated
10/03/2013 Medical Policy Committee review
10/16/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date: 10/2014

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. reference to federal regulations.
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**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. in accordance with nationally accepted standards of medical practice;
B. clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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